The role of contact activation in thrombosis and beyond

Coen Maas

University Medical Center Utrecht, Clinical Chemistry and Haematology, Utrecht, The Netherlands

The contact system is a mysterious enzyme system without a clear physiologic function. It spontaneously initiates coagulation when plasma contacts negatively charged crystalline particles (e.g. kaolin), but is redundant for physiological hemostasis.
Platelet dense granules contain polyphosphate, which acts on blood coagulation and fibrinolysis. Activated platelets drive coagulation in a factor XII-dependent manner and polyphosphate has been identified as a platelet-derived factor XII activator *in vivo*. Agents that block polyphosphate have antithrombotic properties in experimental models for thrombosis. Secreted polyphosphate in the supernatant of activated platelets has a chain length of 60-100 residues. However, these short polymers only have limited potential for activating factor XII. As such, it has remained unclear how platelet polyphosphate could drive factor XII activation in thrombosis. We have now identified that platelets carry and release polyphosphate as crystalline particles that trigger contact system activation in a manner that closely resembles *in vitro* clotting assays.
Besides its role in coagulation, the contact system also produces the short-lived inflammatory peptide bradykinin. It is generally assumed that these functions always take place simultaneously. However, bradykinin is implicated in inflammatory- and severe allergic reactions, without accompanying thrombotic features. This suggests that sophisticated regulatory mechanisms are in place to control the contact system. During coagulation tests *in vitro*, plasma kallikrein (PK) is instrumental in the formation of two-chain activated factor XII (FXIIa). Further cleavage of FXIIa by PK generates smaller active fragments. This eliminates procoagulant activity, but keeps its proinflammatory potential intact. Because of this pronounced role *in vitro*, PK is held exclusively responsible for physiological contact system activation and bradykinin production.
The fibrinolytic system is of high importance for breakdown of fibrin polymers in blood clots. However, its main enzyme plasmin can become active on cells in the complete absence of blood clots for alternative reasons. It was first reported in 1971 that plasmin cleaves and activates Factor XII in a manner that is highly similar to PK. Bradykinin is produced as a result. Several lines of evidence suggest that plasmin is important for activation of the plasma contact system *in vivo*. Firstly, angioedema (bradykinin-driven tissue swelling) is seen as a rare (2.5%) but dangerous side-effect of fibrinolytic therapy in stroke patients. Secondly, fibrinolytic activity is seen in patients with hereditary forms of angioedema (HAE). Selective inhibition of the activation and activity of the fibrinolytic system with soluble lysine analogues is therapeutic in these patients. Additionally, we recently discovered that several distinct mutations in FXII that cause HAE (FXII-HAE) increase the potential for FXII activation by plasmin. When plasmin triggers contact system activation in FXII-HAE plasma, a burst of uncontrolled bradykinin production follows. Based on the combined evidence, we propose that interplay with the fibrinolytic system plays a pivotal role in the physiological production of bradykinin by the contact system.